In September 1999, soon after our discovery of the NEMO protein at Pasteur Institute (Paris) we had an unexpected visit. A shy young scientist, Dr. Asma Smahi, came in the laboratory asking whether she could get a few microliters of our anti-NEMO antibody. When she added that she had walked from the nearby Necker hospital and was working in Prof. Arnold Munnich’s laboratory, well-known for chasing mutated genes in genetic diseases, a “Can you tell us a bit more?” had to be asked. “We have discovered a skin-related pathology caused by a NEMO mutation and I would like to confirm this with an antibody” was her straight response. Luckily I was seated when she pronounced this sentence…

For molecular biologists like us working on this protein and knowing its key function in NF-κB signaling, but having very little knowledge in human genetics I must confess, a disease caused by its mutation and, yet, survival was impossible to conceive. We just missed the key point (that we had learned recently though): The gene encoding NEMO was located on the X chromosome. As will be exposed later in this book, this makes everything possible in females, reconciliating molecular biologists, even the ignorant ones, and human geneticists.

What is related here was the first episode of what would be an exciting journey in the world of NF-κB-related diseases. Identifying NEMO mutations causing this pathology with a weird name, incontinentia pigmenti (“Can you repeat please?”), provided an entry point for understanding how deregulated NF-κB activation would impact on human health. And unexpected findings quickly followed…

Since then, especially during the last 5 years, the field has exploded with the discovery of mutations affecting many other proteins of the NF-κB pathway such as IKK1, IKK2, p100, NIK, etc… This has been mostly due to tremendous progresses accomplished in next-generation sequencing. It is therefore possible to draw at this stage a first picture of how the various components of the NF-κB pathway impact on human health.
In this book, we tried to describe the current state of this field. Exhaustivity is always difficult to reach when the aim is to provide genetic, clinical, and molecular descriptions of pathologies. Therefore, our minimal ambition will be to at least show how complex, fascinating, and informative human genetics can be, even when related to molecular systems that are supposed to be fairly well understood.

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